CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-405

Approval Letter

ANDA 75-405

AUG 31 1999

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated June 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cladribine Injection, 1 mg/mL, 10 mL vial.

Reference is also made to your amendments dated May 10, and August 2, 1999.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is tentatively approved. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product) and is subject to change on the basis of new information that may come to our attention. The listed reference drug product upon which you have based your application, Leustatin Injection of R.W. Johnson Pharmaceutical Research Institute, is subject to a period of orphan drug exclusivity (ODE). Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(D) of the Act until the ODE has expired, i.e., February 26, 2000.

Because the agency is granting a tentative approval for this application, please submit an amendment at least 60-days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and/or controls data as appropriate. An amendment

should be submitted even if none of these changes were made. This submission should be clearly designated in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to agency review before final approval of the application will be made.

The drug product that is the subject of this abbreviated application may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act. Also, until the agency issues the final approval letter, your product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list, (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to February 26, 2000, you should amend your application accordingly.

At the time you amend this application, please contact Michelle Dillahunt, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 28 2000

ANDA 75-405

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated June 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cladribine Injection, 1 mg/mL.

Reference is also made to our Tentative Approval letter dated August 31, 1999, and to your amendments dated December 6, and December 16, 1999.

The listed reference drug product upon which you have based your application, Leustatin Injection, 1 mg/mL, of R.W. Johnson Pharmaceutical Research Institute, was subject to a period of orphan drug exclusivity (ODE) which expired on February 26, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cladribine Injection, 1 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Leustatin® Injection, 1 mg/mL, of R.W. Johnson Pharmaceutical Research Institute).

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaign. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

2/28/00

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-405

FINAL PRINTED LABELING

In these studies, 80% of the patients had not received prior chemotherapy for Hairy Cell Leukemia or had undergone splenectomy as the only prior treatment and were receiving cladribine as a first-line treatment. The remaining 40% of the patients received cladribine as a second-line treatment, having been treated previously with other agents, including α-interferon and/or deoxycoformycin. The overall response rate for patients without prior chemotherapy was 92%, compared with 84% for previously treated patients. Cladribine is active in previously treated patients; however, retrospective analysis suggests that the overall response rate is decreased in patients previously treated with splenectomy or deoxycoformycin and in patients refractory to α-interferon.

OVERALL RESPONSE RATES (CR + nP + PR) TO CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	OVERALL RESPONSE (N=123)	NR + RELAPSE
No Prior Chemotherapy	68/74 92%	6 + 4 14%
Any Prior Chemotherapy	41/49 84%	8 + 3 22%
Previous Splenectomy	32/41* 78%	9 + 1 24%
Previous Interferon	40/48 83%	8 + 3 23%
Interferon Refractory	6/11* 55%	5 + 2 64%
Previous Deoxycoformycin	3/6* 50%	3 + 1 66%

NR = No Response
*P<0.05

After reversible decline, normalization of peripheral blood counts (Hemoglobin >12 g/dL, Platelets >100 x 10^9/L, Absolute Neutrophil Count (ANC) >1500 x 10^9/L) was achieved by 92% of evaluable patients. The median time to normalization of peripheral counts was 9 weeks from the start of treatment (Range: 2 to 72). The median time to normalization of Platelet Count was 2 weeks, the median time to normalization of ANC was 5 weeks and the median time to normalization of Hemoglobin was 8 weeks. With normalization of Platelet Count and Hemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in those patients with complete response. Platelet recovery may be delayed in a minority of patients with severe baseline thrombocytopenia. Corresponding to normalization of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding cladribine therapy. See also **WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS.**

CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA TIME TO NORMALIZATION OF PERIPHERAL BLOOD COUNTS

Parameter	Median Time to Normalization of Count*
Platelet Count	2 weeks
Absolute Neutrophil Count	5 weeks
Hemoglobin	8 weeks
ANC, Hemoglobin and Platelet Count	9 weeks

*Day 1 = First day of infusion

For patients achieving a complete response, the median time to response (i.e., absence of hairy cells in bone marrow and peripheral blood together with normalization of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalization, the median time to complete response may actually be shorter than that which was recorded. At the time of data cut- off, the median duration of complete response was greater than 8 months and ranged to 25+ months. Among 93 responding patients, seven had shown evidence of disease progression at the time of the data cut-off. In four of these patients, disease was limited to the bone marrow without peripheral blood abnormalities (pathologic progression), while in three patients there were also peripheral blood abnormalities (clinical progression). Seven patients who did not respond to a first course of cladribine received a second course of therapy. In the five patients who had adequate follow-up, additional courses did not appear to improve their overall response.

INDICATIONS AND USAGE

Cladribine is indicated for the treatment of active Hairy Cell Leukemia as defined by clinically significant anemia, neutropenia, thrombocytopenia or disease-related symptoms.

CONTRAINDICATIONS

Cladribine is contraindicated in those patients who are hypersensitive to this drug or any of its components.

WARNINGS

Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, has been commonly observed in patients treated with cladribine, especially at high doses. At initiation of treatment, most patients in the clinical studies had hematologic impairment as a manifestation of active Hairy Cell Leukemia. Following treatment with cladribine, further hematologic impairment occurred before recovery of peripheral blood counts began. During the first two weeks after treatment initiation, mean Platelet Count, ANC, and Hemoglobin concentration declined and subsequently increased with normalization of mean counts by Day 12, Week 5 and Week 8, respectively. The myelosuppressive effects of cladribine were most notable during the first month following treatment. Forty-four percent (44%) of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful hematologic monitoring, especially during the first 4 to 8 weeks after treatment with cladribine, is recommended. See **PRECAUTIONS.**

Fever (T ≥ 100 F) was associated with the use of cladribine in approximately two-thirds of patients (131/196) in the first month of therapy. Virtually all of these patients were treated empirically with parenteral antibiotics. Overall, 47% (93/196) of all patients had fever in the setting of neutropenia (ANC ≤ 1000), including 62 patients (32%) with severe neutropenia (i.e., ANC ≤ 500).

In a Phase I investigational study using cladribine in high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia) as part of a bone marrow transplant conditioning regimen, which also included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed. Thirty-one (31) poor-risk patients with drug-resistant acute leukemia in relapse (29 cases) or non-Hodgkins Lymphoma (2 cases) received cladribine for 7 to 14 days prior to bone marrow transplantation. During infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumor cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with cladribine, 6 patients (19%) developed manifestations of renal dysfunction (e.g., acidosis, anuria, elevated serum creatinine, etc.) and 5 required dialysis. Several of these patients were also being treated with other medications having known nephrotoxic potential. Renal dysfunction was reversible in 2 of these patients. In the 4 patients whose renal function had not recovered at the time of death, autopsies were performed; in 2 of these, evidence of tubular damage was noted. Eleven (11) patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterized by progressive irreversible motor weakness (paraparesis/quadriparesis), of the upper and/or lower extremities, first noted 35 to 84 days after starting high dose therapy with cladribine. Non-invasive testing (electromyography and nerve conduction studies) was consistent with demyelinating disease. Severe neurologic toxicity has also been noted with high doses of another drug in this class.

Axonal peripheral polyneurophathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

In patients with Hairy Cell Leukemia treated with the recommended treatment regimen (0.09 mg/kg/day for 7 consecutive days), there have been no reports of nephrologic toxicities.

Of the 196 Hairy Cell Leukemia patients entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following cladribine therapy. Of the 6 deaths, 5 occurred in previously treated patients who were Refractory to α-*interferon*.

Benzyl alcohol is a constituent of the recommended diluent for the 7-day infusion solution. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. See **DOSAGE AND ADMINISTRATION.**

Pregnancy Category D: Cladribine should not be given during pregnancy.

Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m²) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3 mg/kg/day (9 mg/m²). Fetal death and malformations were observed in rabbits that received 3 mg/kg/day

(33 mg/m²). No fetal effects were seen in mice at 0.5 mg/kg/day (1.5 mg/m²) or in rabbits at 1 mg/kg/day (11 mg/m²).

Although there is no evidence of teratogenicity in humans due to cladribine, other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. Cladribine has been shown to be embryotoxic in mice when given at doses equivalent to the recommended dose.

There are no adequate and well controlled studies in pregnant women. If cladribine is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS

General: Cladribine is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered only under the supervision of a physician experienced with the use of cancer chemotherapeutic agents. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Periodic assessment of peripheral blood counts, particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (e.g., infection or bleeding). As with other potent chemotherapeutic agents, monitoring of renal and hepatic function is also recommended, especially in patients with underlying kidney or liver dysfunction. See **WARNINGS** and **ADVERSE REACTIONS.**

Fever was a frequently observed side effect during the first month on study. Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics should be initiated as clinically indicated. Although 69% of patients developed fevers, less the 1/3 of febrile events were associated with documented infection.

Given the known myelosuppressive effects of cladribine, practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections. See **WARNINGS** and **ADVERSE REACTIONS.**

There are inadequate data on dosing of patients with renal or hepatic insufficiency. Development of acute renal insufficiency in some patients receiving high doses of cladribine has been described. Until more information is available, caution is advised when administering the drug to patients with known or suspected renal or hepatic insufficiency. See **WARNINGS.**

Rare cases of tumor lysis syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumor burden.

Cladribine must be diluted in designated intravenous solutions prior to administration. See **DOSAGE AND ADMINISTRATION.**

Laboratory Tests: During and following treatment, the patient's hematologic profile should be monitored regularly to determine the degree of hematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean Platelet Count reached 100 x 10⁹/L by Day 12, the mean Absolute Neutrophil Count reached 1500 x 10⁹/L by Week 5 and the mean Hemoglobin reached 12 g/dL by Week 8. After peripheral counts have normalized, bone marrow aspiration and biopsy should be performed to confirm response to treatment with cladribine. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

Drug Interactions: There are no known drug interactions with cladribine. Caution should be exercised if cladribine is administered before, after, or in conjunction with other drugs known to cause immunosuppression or myelosuppression. See **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine.

As expected for compounds in this class, the actions of cladribine yield DNA damage. In mammalian cells in culture, cladribine caused the accumulation of DNA strand breaks. Cladribine was also incorporated into DNA of human lymphoblastic leukemia cells. Cladribine was not mutagenic *in vitro* (Ames and Chinese hamster ovary cell gene mutation tests) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures. However, cladribine was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test).

When administered intravenously to Cynomolgus monkeys, cladribine has been shown to cause suppression of rapidly generating cells, including testicular cells. The effect on human fertility is unknown.

Pregnancy: Teratogenic Effects: Pregnancy Category D: See **WARNINGS.**

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cladribine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. In a Phase I study involving patients 1 to 21 years old with relapsed acute leukemia, cladribine was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m²/day for 5 days (one-half to twice the dose recommended in Hairy Cell Leukemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose (10.7 mg/m²/day), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted in this study.[1] See **WARNINGS** and **ADVERSE REACTIONS.**

ADVERSE REACTIONS

Safety data are based on 198 patients with Hairy Cell Leukemia: the original cohort of 124 patients plus and additional 72 patients enrolled at the same two centers after the original enrollment cutoff. In Month 1 of the Hairy Cell Leukemia clinical trials, severe neutropenia was noted in 70% of patients, fever in 69%, and infection was documented in 28%. Other adverse experiences reported frequently during the first 14 days after initiating treatment included: fatigue (45%), nausea (28%), rash (27%), headache (22%) and injection site reactions (19%). Most non-hematologic adverse experiences were mild to moderate in severity.

Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia (ANC < 500 x 10⁹/L) was noted in 70% of patients, compared with 26% in whom it was present initially. Severe anemia (Hemoglobin <8.5 g/dL) developed in 37% of patients, compared with 10% initially and thrombocytopenia (Platelets < 20 x 10⁹/L) developed in 12% of patients, compared to 4% in whom it was noted initially.

During the first month, 54 of 198 patients (28%) exhibited documented evidence of infection. Serious infections (e.g., septicemia, pneumonia) were reported in 6% of all patients; the remainder were mild or moderate. Several deaths were attributable to infection and/or complications related to the underlying disease. During the second month, the overall rate of documented infection was 6%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding cladribine therapy.

During the first month, 11% of patients experienced severe fever (i.e., ≥104°F). Documented infections were noted in fewer than one-third of febrile episodes. Of the 198 patients studied, 19 were noted to have a documented infection in the month prior to treatment. In the month following treatment, there were 54 episodes of documented infection: 23 (42%) were bacterial, 11 (20%) were viral and 11 (20%) were fungal. Seven (7) of 11 documented episodes of herpes zoster occurred during the month following treatment. Fourteen (14) of 16 episodes of documented fungal infections occurred in the first two months following treatment. Virtually all of these patients were treated empirically with antibiotics. See **WARNINGS** and **PRECAUTIONS.**

Analysis of lymphocyte subsets indicates that treatment with cladribine is associated with prolonged depression of the CD4 counts. Prior to treatment, the mean CD4 count was 766/uL. The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was 272/uL. Fifteen (15) months after treatment, mean CD4 counts remained below 500/uL. CD8 counts behaved similarly, though increasing counts were observed after 9 months. The clinical significance of the prolonged CD4 lymphopenia is unclear.

Another event of unknown clinical significance includes the observation of prolonged bone marrow hypocellularity. Bone marrow cellularity of <35% was noted after 4 months in 42 of 124 patients (34%) treated in the two pivotal trials. This hypocellularity was noted as late as day 1010. It is not known whether the hypocellularity is the result of disease related marrow fibrosis or if it is the result of cladribine toxicity. There was no apparent clinical effect on the peripheral blood counts.

The vast majority of rashes were mild and occurred in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause rash.

Most episodes of nausea were mild, not accompanied by vomiting, and did not require treatment with antiemetics. In patients requiring antiemetics, nausea was easily controlled, most frequently with chlorpromazine.

Adverse reactions reported during the first 2 weeks following treatment initiation (regardless of relationship to drug) by >5% of patients included:

Body as a Whole: fever (69%), fatigue (45%), chills (9%), asthenia (9%), diaphoresis (9%), malaise (7%), trunk pain (6%)

Gastrointestinal: nausea (28%), decreased appetite (17%), vomiting (13%), diarrhea (10%), constipation (9%), abdominal pain (6%)

Hemic/Lymphatic: purpura (10%), petechiae (8%), epistaxis (5%)

Nervous System: headache (22%), dizziness (9%), insomnia (7%)

Cardiovascular System: edema (6%), tachycardia (6%)

Respiratory System: abnormal breath sounds (11%), cough (10%), abnormal chest sounds (9%), shortness of breath (7%)

Skin/Subcutaneous Tissue: rash (27%), injection site reactions (19%), pruritis (6%), pain (6%), erythema (6%)

Musculoskeletal System: myalgia (7%), arthralgia (5%)

Adverse experiences related to intravenous administration included: injection site reactions (9%) (i.e., redness, swelling, pain), thrombosis (2%), phlebitis (2%) and a broken catheter (1%).

These appear to be related to the infusion procedure and/or indwelling catheter, rather than the medication or the vehicle. From Day 15 to the last follow-up visit, the only events reported by >5% of patients were: fatigue (11%), rash (10%), headache (7%), cough (7%), and malaise (5%).

For a description of adverse reactions associated with use of high doses in non-Hairy Cell Leukemia patients, see **WARNINGS.**

The following additional adverse events have been reported since the drug became commercially available. These adverse events have been reported primarily in patients who received multiple courses of cladribine:

Hematologic: bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia; hemolytic anemia, which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment.

Hepatic: reversible, generally mild increases in bilirubin and transaminases.

Nervous System: Neurological toxicity; however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.
Respiratory System: pulmonary interstitial infiltrates; in most cases, an infectious etiology was identified.
Skin/Subcutaneous: urticaria, hypereosinophilia: In isolated cases Stevens-Johnson and toxic epidermal necrolysis have been reported in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause these syndromes.
Opportunistic infections have occurred in the acute phase of treatment due to the immunosuppression mediated by cladribine.

OVERDOSAGE

High doses of cladribine have been associated with: irreversible neurologic toxicity (paraparesis/quadriparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anemia and thrombocytopenia. See **WARNINGS**. There is no known specific antidote to overdosage. Treatment of overdosage consists of discontinuation of cladribine, careful observation and appropriate supportive measures. It is not known whether the drug can be removed from the circulation by dialysis or hemofiltration.

DOSAGE AND ADMINISTRATION

Usual Dose:

The recommended dose and schedule of cladribine for active Hairy Cell Leukemia is as a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. Deviations from this dosage regimen are not advised. If the patient does not respond to the initial course of cladribine for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs. See **WARNINGS**.

Specific risk factors predisposing to increased toxicity from cladribine have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any etiology. Patients should be monitored closely for hematologic and non-hematologic toxicity. See **WARNINGS** and **PRECAUTIONS**.

Preparation and Administration of Intravenous Solutions:

Cladribine must be diluted with the designated diluent prior to administration. Since the drug product does not contain any antimicrobial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of cladribine solutions.
To prepare a single daily dose: Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of cladribine to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection. Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days. The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine. Admixtures of cladribine are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in Baxter Viaflex®† PVC infusion containers. Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised.

	Dose of Cladribine Injection	Recommended Diluent	Quantity of Diluent
24 hour infusion method	1 (dry) x 0.09 mg/kg	0.9% Sodium Chloride Injection	500 mL

To prepare a 7 day infusion: The 7 day infusion solution should only be prepared with Bacteriostatic 0.9% Sodium Chloride Injection (0.9% benzyl alcohol preserved). In order to minimize the risk of microbial contamination, both cladribine injection and the diluent should be passed through a sterile 0.22µ disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of cladribine (7 days x 0.09 mg/kg or mL/kg) to the infusion reservoir through the sterile filter. Then add a calculated amount of Bacteriostatic 0.9% Sodium Chloride Injection (0.9% benzyl alcohol preserved) also through the filter to bring the total volume of the solution to 100 mL. After completing solution preparation, clamp off the line, disconnect and discard the filter. Aseptically aspirate air bubbles from the reservoir as necessary using the syringe and a dry second sterile filter or a sterile vent filter assembly. Reclamp the line and discard the syringe and filter assembly. Infuse continuously over 7 days. Solutions prepared with Bacteriostatic Sodium Chloride Injection for individuals weighing more than 65 kg may have reduced preservative effectiveness due to greater dilution of the benzyl alcohol preservative. Admixtures for the 7 day infusion have demonstrated acceptable chemical and physical stability for at least 7 days in the SIMS Deltec MEDICATION CASSETTE™ Reservoir ‡.

	Dose of Cladribine Injection	Recommended Diluent	Quantity of Diluent
7 day infusion method (use sterile 0.22µ filter when preparing infusion solution)	7 (days) x 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection (0.9% benzyl alcohol)	q.s. to 100 mL

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised. Solutions containing cladribine should not be mixed with other intravenous drugs or additives or infused simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates. See **WARNINGS**.

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of cladribine should be administered promptly or stored in the refrigerator (2° to 8° C) for no more than 8 hours prior to start of administration. Vials of cladribine are for single-use only. Any unused portion should be discarded in an appropriate manner. See **Handling and Disposal**.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of cladribine to low temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

Chemical Stability of Vials:

When stored in refrigerated conditions between 2° to 8° C (36° to 46° F) protected from light, unopened vials of cladribine are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. DO NOT heat or microwave. Once thawed, the vial of cladribine is stable until expiry if refrigerated. DO NOT refreeze. Once diluted, solutions containing cladribine should be administered promptly or stored in the refrigerator (2° to 8° C) for no more than 8 hours prior to administration.

Handling and Disposal:

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering cladribine. The use of disposable gloves and protective garments is recommended. If cladribine contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

HOW SUPPLIED

Cladribine Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine as 10 mL filled into a single-use clear flint glass 20 mL vial, individually boxed. **NDC 66298-124-01**
Store refrigerated 2° to 8° C (36° to 46° F). Protect from light during storage.

REFERENCES

1. Santana VM, Mirro J, Harwood FC *et al*: A Phase I Clinical Trial of 2-Chloro-deoxyadenosine in Pediatric Patients with Acute Leukemia. *J. Clin. Oncol.* 1991; 9: 416.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents; US Government Printing Office, Washington, DC 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA* 1985; 253 (11): 1590-1592.
4. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts, 02115.
5. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.
6. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians* 1983; Sept/Oct. 258-263.
7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm* 1986; 43:1193-1204.

† Viaflex® containers, manufactured by Baxter Healthcare Corporation - Code No. 2B8013 (tested in 1991)
‡ MEDICATION CASSETTE™ Reservoir, manufactured by SIMS Deltec, Inc. - Reorder No. 802100A (tested in 1991)

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146
January 2000

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146
CLD-P00

BEDFORD LABORATORIES™

CLADRIBINE INJECTION

Rx ONLY.

For Intravenous Infusion Only

WARNINGS

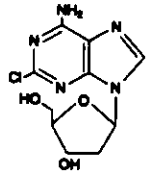
Cladribine injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Serious neurological toxicity (including irreversible paraparesis and quadraparesis) has been reported in patients who received cladribine injection by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia). Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Acute nephrotoxicity has been observed with high doses of cladribine (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies.

DESCRIPTION

Cladribine injection (also commonly known as 2-chloro-2'-deoxy-β-D-adenosine) is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. Cladribine injection is available in single-use vials containing 10 mg (1 mg/mL) of cladribine, a chlorinated purine nucleoside analog. Each mL of cladribine injection contains 1 mg of the active ingredient and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3 ± 0.3.

The chemical name for cladribine is 2-chloro-6-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine and the structure is represented below:



Molecular Formula = $C_{10}H_{12}ClN_5O_3$ Molecular Weight = 285.69

CLINICAL PHARMACOLOGY

Cellular Resistance and Sensitivity:

The selective toxicity of 2-chloro-2'-deoxy-β-D-adenosine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2'-deoxy-β-D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2'-deoxy-β-D-adenosine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2'-deoxy-β-D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2'-deoxy-β-D-adenosine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2'-deoxy-β-D-adenosine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair.

HUMAN PHARMACOLOGY

In a clinical investigation, 17 patients with Hairy Cell Leukemia and normal renal function were treated for 7 days with the recommended treatment regimen of cladribine (0.09 mg/kg/day) by continuous intravenous infusion. The mean steady-state serum concentration was estimated to be 5.7 ng/mL with an estimated systemic clearance of 663.5 mL/h/kg when cladribine was given by continuous infusion over 7 days. In Hairy Cell Leukemia patients, there does not appear to be a relationship between serum concentrations and ultimate clinical outcome.

In another study, 8 patients with hematologic malignancies received a two (2) hour infusion of cladribine (0.12 mg/kg). The mean end-of-infusion plasma cladribine concentration was 48 ± 19 ng/mL. For 5 of these patients, the disappearance of cladribine could be described by either a biphasic or triphasic decline. For these patients with normal renal function, the mean terminal half-life was 5.4 hours. Mean values for clearance and steady-state volume of distribution were 978 ± 422 mL/h/kg and 4.5 ± 2.8 L/kg, respectively.

Plasma concentrations are reported to decline multi-exponentially after intravenous infusions with terminal half-lives ranging from approximately 3 to 22 hours. In general, the apparent volume of distribution of cladribine is very large (mean approximately 9 L/kg), indicating an extensive distribution of cladribine in body tissues. The mean half-life of cladribine in leukemic cells has been reported to be 23 hours.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma.

Cladribine is bound approximately 20% to plasma proteins.

Except for some understanding of the mechanism of cellular toxicity, no other information is available on the metabolism of cladribine in humans. An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumors during a 5-day continuous intravenous infusion of 3.5 to 8.1 mg/m²/day of cladribine. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

Two single-center open label studies of cladribine have been conducted in patients with Hairy Cell Leukemia with evidence of active disease requiring therapy. In the study conducted at the Scripps Clinic and Research Foundation (Study A), 89 patients were treated with a single course of cladribine given by continuous intravenous infusion for 7 days at a dose of 0.09 mg/kg/day. In the study conducted at the M.D. Anderson Cancer Center (Study B), 35 patients were treated with a 7 day continuous intravenous infusion of cladribine at a comparable dose of 3.6 mg/m²/day. A complete response (CR) required clearing of the peripheral blood and bone marrow of hairy cells and recovery of the hemoglobin to 12 g/dL, platelet count to 100 x 10⁹/L, and absolute neutrophil count to 1500 x 10⁹/L. A good partial response (GPR) required the same hematologic parameters as a complete response, and that fewer than 5% hairy cells remain in the bone marrow. A partial response (PR) required that hairy cells in the bone marrow be decreased by at least 50% from baseline and the same response for hematologic parameters as for complete response. A pathologic relapse was defined as an increase in bone marrow hairy cells to 25% of pretreatment levels. A clinical relapse was defined as the recurrence of cytopenias, specifically, decreases in hemoglobin ≥ 2 g/dL, ANC ≥ 25% or platelet counts ≥ 50,000. Patients who met the criteria for a complete response but subsequently were found to have evidence of bone marrow hairy cells (<25% of pretreatment levels) were reclassified as partial responses and were not considered to be complete responses with relapse.

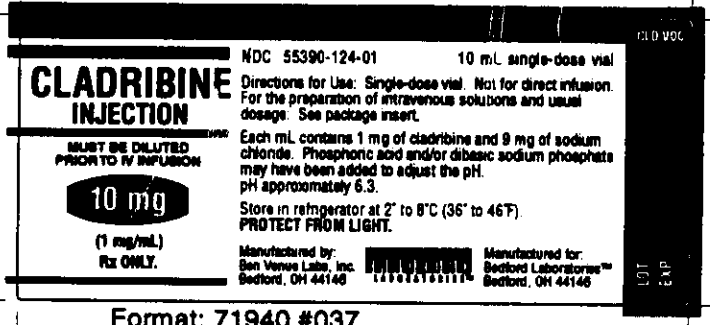
Among patients evaluable for efficacy (N=106), using the hematologic and bone marrow response criteria described above, the complete response rates in patients treated with cladribine were 85% and 88% for Study A and Study B, respectively, yielding a combined complete response rate of 86%. Overall response rates (i.e., Complete plus Good Partial plus Partial Responses) were 89% and 86% in Study A and Study B, respectively, for a combined overall response rate of 88% in evaluable patients treated with cladribine.

Using an intent-to-treat analysis (N=123) and further requiring no evidence of splenomegaly as a criterion for CR (i.e., no palpable spleen on physical examination and ≤ 13 cm on CT scan), the complete response rates for Study A and Study B were 54% and 53%, respectively, giving a combined CR rate of 54%. The overall response rates (CR + GPR + PR) were 90% and 85%, for Studies A and B, respectively, yielding a combined overall response rate of 89%.

RESPONSE RATES TO CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	CR	Overall
Evaluable Patients N=106	86%	88%
Intent-to-treat Population N=123	54%	89%

Note: Keyline does not print.



Format: 71940 #037
1.5" x 3.5"
PMS Black, PMS 032 Red, PMS 3292 Green

OMG

FEB 28

Each mL contains 1 mg of cladribine and 9 mg of sodium chloride. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH. pH approximately 6.3.

Manufactured by:
Ben Venue Labs, Inc.,
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™,
Bedford, OH 44146

NDC 55390-124-01
10 mL single-dose vial

CLADRIBINE
INJECTION

MUST BE DILUTED PRIOR TO IV INFUSION

10 mg

(1 mg/mL)

Rx ONLY.

BEDFORD LABORATORIES™

Directions for Use:
Single-dose vial. Not for direct infusion. For the preparation of intravenous solutions and usual dosage: See package insert.

Store in refrigerator at 2° to 8°C (36° to 46°F).

PROTECT FROM LIGHT.
Retain in carton until time of use.

NDC 55390-124-01
10 mL single-dose vial

CLADRIBINE
INJECTION

MUST BE DILUTED PRIOR TO IV INFUSION

10 mg

(1 mg/mL)

Rx ONLY.

BEDFORD LABORATORIES™

55390-124-01

LOT
EXP

CLD-C00

Format Number: 71939 #014A
Black
3292 Green
032 Red

Prepared by
Mark Zarnstorff
Checked by

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-405

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 5 Cycle Number: N/A (ANDA has been tentatively approved)

2. ANDA # 75-405

METHODS VALIDATION DEFICIENCIES

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10-mL fill in 20-mL vial

4. LEGAL BASIS FOR SUBMISSION
Leustatin Inj, NDA 20-229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:

06/29/98 Original submission

Vol. A2.1:

03/23/99 Minor amendment - included revised analytical methods
04/01/99 MVP was submitted
08/31/99 ANDA 75-405 was tentatively approved in the absence of methods validation.
10/27/99 An MV Report dated 10/22/99 was received from the FDA Pacific Regional Laboratory Northwest, Seattle. The lab considered Bedford's methods satisfactory with modifications.
12/06/99 Minor amendment in response to tentative approval letter of 8/31/99 - no changes in CMC or labeling, 12 copies of FPL submitted
12/08/99 NA Minor facsimile for MV deficiencies
12/09/99 Telecon re Deficiency #1.b of 12/08/99
12/16/99 Minor amendment in response to 12/08 **(the subject of this review)**

17. COMMENTS

31. SAMPLES AND RESULTS

The responses to the MV deficiencies are **satisfactory.**

32. LABELING

The labeling submitted 12/6/99 was found **satisfactory** by Teresa Watkins 12/10/99.

18. CONCLUSIONS AND RECOMMENDATIONS

On 08/31/99, ANDA 75-405 was tentatively approved in the absence of methods validation. ANDA 75-405 **can be TENTATIVELY APPROVED** again, or it appears it can be fully approved on 2/26/2000.

Note: The DS and DP continue to lack inclusion in USP 24. DMF 13006 for the DS has not been amended since the ANDA was tentatively approved.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 12/30/99

Page(s) 3

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Chemistry Review #5

12/30/99

Page(s) 2

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releasable.

12/8/99

Chemistry Comment

#38

1. CHEMISTRY REVIEW NO. 4 Cycle Number: Out of Cycle

2. ANDA # 75-405

ADDENDUM FOR METHODS VALIDATION DEFICIENCIES

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10-mL fill in 20-mL vial

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20-229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:

06/29/98 Original submission

Vol. A2.1:

03/23/99 Minor amendment

17. COMMENTS

31. SAMPLES AND RESULTS

ANDA 75-405 was tentatively approved 8/31/99 in the absence of methods validation. An MV Report dated 10/22/99 was received from the FDA Pacific Regional Laboratory Northwest, Seattle, on 10/27/99. The lab considered Bedford's methods **satisfactory with modifications (lab classification 2).**

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **NOT APPROVED - MINOR AMENDMENT** requested, because of deficiencies in analytical methods.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 11/19/99

Page(s) 6

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Chemistry Review #4

11/19/99

1. CHEMISTRY REVIEW NO. 4 Cycle Number: 3

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:

06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

Vol. A2.1:

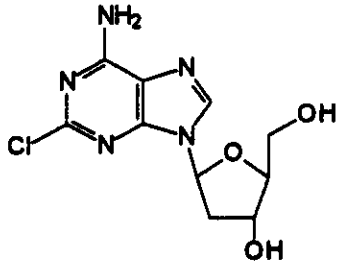
03/23/99 Minor amendment
04/27/99 NA Minor fax from FDA

05/10/99 Minor amendment
07/21/99 NA Facsimile fax from FDA
08/02/99 Facsimile amendment - micro response

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

All chemistry deficiencies in Points 20 through 30 have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The aseptic processing was found **satisfactory** by Dr. Lynne Ensor 08/06/99 per email. The review is waiting signature.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 10. Methods Validation has been started, but not completed, per E-mail from Tom Savage 8/10/99.
If an MV report has not been received from the Seattle lab by the time the approval package is ready for final sign-off, the following New Comment should be sent to Bedford Labs: Please provide a commitment to cooperate fully with the Agency regarding any issues which might arise during FDA validation of your analytical methods.

32. LABELING

EPL submitted 3/23/99. Tentatively approved 4/5/99.

33. ESTABLISHMENT INSPECTION

Facilities were found acceptable 8/24/98. **A new EER should be requested, because the approval package will probably not get all the required signatures by 8/24/99.**

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **ready for approval**. Methods validation has not been completed, as of 8/10/99.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 8/10/99

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Chemistry Review #4

9/10/99

Page(s) 1

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releasable.

7/21/99

Chemistry Comment

#38

1. CHEMISTRY REVIEW NO. 3 Cycle Number: 3

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

ADDENDUM

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:
06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

Vol. A2.1:

03/23/99 Minor amendment
04/27/99 NA Minor fax from FDA
05/10/99 Minor amendment

17. COMMENTS

This review was CHEMISTRY CLOSED on 5/24/99, awaiting a microbiology review, and MV by an FDA lab.

The aseptic processing was found **not satisfactory** 6/11/99 by Lynne A. Ensor, Ph.D. Deficiencies are being faxed to Bedford.

Samples were transferred from PHI-DO to PRL-NW, Seattle, 5/6/99. I called Tom Savage in Seattle 7/13/99. He estimated the lab work **might be done in another three weeks.**

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **ready for approval except for microbiology and methods validation. A facsimile amendment** is being requested.

19. REVIEWER: ADDENDUM COMPLETED:

Eugene L. Schaefer, Ph.D. 7/13/99

Page(s) 1

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7/20/99

Chemistry Comment

38

1. CHEMISTRY REVIEW NO. 3 Cycle Number: 3

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

CHEMISTRY CLOSE

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:
06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

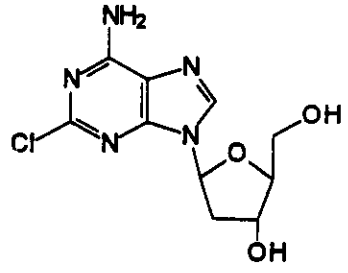
Vol. A2.1:

03/23/99 Minor amendment
04/27/99 NA Minor fax from FDA
05/10/99 Minor amendment

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

All chemistry deficiencies in Points 20 through 30 have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The review of aseptic processing has not been completed, as of 5/21/99.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 10. Methods Validation has been scheduled. **Samples were transferred from PHI-DO to PRL-NW, Seattle, 5/6/99.**

32. LABELING

FPL submitted 3/23/99. Tentatively approved 4/5/99.

33. ESTABLISHMENT INSPECTION

Facilities were found acceptable 8/24/98.

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **ready for approval except for microbiology and methods validation.**

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 5/21/99

Page(s) 14

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Chemistry Review HJ

5/21/99

Page(s) 2

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4/27/99

Chemistry Comment

#38

1. CHEMISTRY REVIEW NO. 2 Cycle Number: 2

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC

Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)

N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

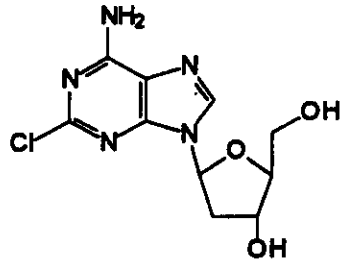
Vol. A1.1 and A1.2:
06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

Vol. A2.1:
03/23/99 Minor amendment

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

22, 28.B, 29.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The review of aseptic processing has not been completed, as of 3/31/99.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 9. The analytical issues have been resolved, and Methods Validation is being scheduled.

32. LABELING

Not satisfactory 9/23/98. FPL submitted 3/23/99. Not reviewed, as of 4/1/99.

33. ESTABLISHMENT INSPECTION

Facilities were found acceptable 8/24/98.

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **NOT APPROVED - MINOR AMENDMENT** requested.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 4/1/99

Page(s) 16

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releasable.

Chemistry Review #2

4/1/99

Page(s) 3

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Information and are not

releasable.

2/12/99

Chemistry Comments

#3P

1. **CHEMISTRY REVIEW NO.** 1 Cycle Number: 1

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC

Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)

N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

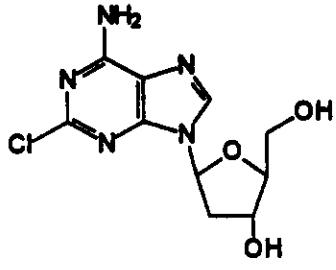
Vol. A1.1 and A1.2:

06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

22, 23.A, 28.B, and 29.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The review of aseptic processing has not been completed, as of 1/26/99.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 9. Methods Validation will be scheduled when the analytical issues have been resolved.

32. LABELING

Not satisfactory 9/23/98, but FPL requested.

33. ESTABLISHMENT INSPECTION

EER submitted 7/31/98.

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **NOT APPROVED - MINOR AMENDMENT** requested.

19. REVIEWER:	DATE COMPLETED:	REVISED:
Eugene L. Schaefer, Ph.D.	1/26/99	1/28/99

Page(s) 18

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Commercial/Confidential

Information and are not

releasable.

Chemistry Review #1

1/20/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-405

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection
1 mg/ml

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours.

/S/

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # 75-405 SPONSOR: Bedford Laboratories.
DRUG AND DOSAGE FORM: Cladribine Injection
Strength(s): 1 mg/ml
Type of Study: SD SDF MULT OTHER
X

STUDY SITE: N/A
STUDY SUMMARY: N/A
FORMULATION: Acceptable
Waiver is granted.

PRIMARY REVIEWER: Marnata S. Gokhale, Ph.D. BRANCH: III
INITIAL /S/ DATE 9/24/98

TEAM LEADER: Barbara M. Davit, Ph.D. BRANCH: III
INITIAL _____ Date 9/24/98

DIRECTOR: Dale P. Conner, D.Pharm.
DIVISION OF BIOEQUIVALENCE
INITIAL /S/ DATE 9/24/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL _____ DATE _____

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # 75-405 SPONSOR: Bedford Laboratories.
DRUG AND DOSAGE FORM: Cladribine Injection
Strength(s): 1 mg/ml
Type of Study: SD SDF MULT OTHER
X

STUDY SITE: N/A
STUDY SUMMARY: N/A
FORMULATION: Acceptable
Waiver is granted.

PRIMARY REVIEWER: Mamata S. Gokhale. Ph.D. BRANCH: III
INITIAL MSG DATE 9/24/98

TEAM LEADER: Barbara M. Davit Ph.D. BRANCH: III
INITIAL _____ Date _____

DIRECTOR: Dale P. Conner, D.Pharm.
DIVISION OF BIOEQUIVALENCE
INITIAL _____ DATE 9/24/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL _____ DATE _____

Cladribine Injection
1 mg/ml, 10 ml vial
ANDA # 75-405
Reviewer: Mamata S. Gokhale

Bedford Laboratories.
Division of Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, Ohio 44146

x:\new\firmsam\bedford\ltrs&rev\75405w.698.doc Submission Date: June 29, 1998

Review of a Waiver Request

Background

1) The firm has submitted a request for a waiver of in vivo bioavailability/bioequivalance study requirements based on 21 CFR 320.22(b)(1) for its proposed product Cladribine Injection, 1 mg/ml, 10 ml vial. The reference listed product is Leustatin® Injection, supplied in vials as 1 mg/ml (NDA #N20229 001, granted to Johnson RW) manufactured by Ortho Biotech Inc.
2) Cladribine is a synthetic antineoplastic agent indicated for the treatment of acute Hairy Cell Leukemia as defined by clinically significant anemia, neutropenia, thrombocytopenia or disease related symptoms. This purine nucleoside analog exerts cytotoxicity towards dividing as well as quiescent lymphocytes and monocytes by inhibiting both DNA synthesis and repair.
3) The reference product, Leustatin® Injection, 1 mg/ml, is to be administered by the intravenous route (continuous infusion). The test product, Cladribine Injection, 1 mg/ml, is proposed to be administered by similar route.

Formulation Comparison

Comparative compositions of test and reference listed products as specified in the package insert:

Comments

1) The proposed product is a parenteral solution intended for administration solely by injection by the intravenous route.
2) The active ingredient, route of administration, dosage form and strength of the test product are same as those of the reference listed product.
3) All ingredients in test and reference products are qualitatively and quantitatively the same.

Recommendations

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories demonstrates that Cladribine injection, 1 mg/ml, falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of an *in vivo* bioequivalence study requirement for Cladribine injection, 1 mg/ml, is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Leustatin® Injection, 1 mg/ml manufactured by Ortho Biotech Inc.

Mamata S. Gokhale, Ph.D.
Review Branch III
Division of Bioequivalence

/S/

for RD INITIALED BDAVIT
FT INITIALED BDAVIT

/S/ Date 9/24/98

for Concur: /S/ Date 9/24/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection
1 mg/ml

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-405

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #2
August 5, 1999

A. 1. **ANDA: 75-405**

APPLICANT: Bedford Laboratories
300 Northfield Road
Bedford, OH 44146

2. PRODUCT NAME: Cladribine Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 10mL (at 1 mg/mL) in 20 cc vials, intravenous injection, single dose vial

4. METHOD(S) OF STERILIZATION: **Aseptically filled.**

5. PHARMACOLOGICAL CATEGORY: synthetic antineoplastic agent for treatment of Hairy Cell Leukemia

B. 1. DATE OF INITIAL SUBMISSION: June 29, 1998
(Received June 30,1998)

2. DATE OF AMENDMENTS: August 2,1999
Subject of this Review (Received August 3, 1999)

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: August 5,1999

C. REMARKS: The chemistry review is complete (5/21/99).

D. CONCLUSIONS: The submission **is recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic processing are provided in "E. Review Notes".

Lynne A. Ensor 8/5/99
Lynne A. Ensor, Ph. D.

cc:

8/10/99

75405a

Page(s) 4

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Information and are not

releasable.

Micro Review #2

8/5/99

Microbiology Comments to be Provided to the Applicant

ANDA: 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection, 10mL (at 1 mg/mL) in 20cc vials

A. Microbiology Deficiencies:

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Micro Review #1

MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #1
June 11, 1999

A. 1. **ANDA: 75-405**

APPLICANT: Bedford Laboratories
300 Northfield Road
Bedford, OH 44146

2. PRODUCT NAME: Cladribine Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 10mL (at 1 mg/mL) in 20 cc vials, intravenous injection, single dose vial

4. METHOD(S) OF STERILIZATION: **Aseptically filled.**

5. PHARMACOLOGICAL CATEGORY: synthetic antineoplastic agent for treatment of Hairy Cell Leukemia

B. 1. DATE OF INITIAL SUBMISSION: **June 29, 1998**
Subject of this Review (Received June 30, 1998)

2. DATE OF AMENDMENTS: 7/14/98 - labeling deficiencies
3/23/99 - Chemistry deficiencies
5/10/99 - Chemistry deficiencies

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: June 3,1999

C. REMARKS: The chemistry review is complete (5/21/99).

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic processing are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

Lynne A. Ensor, Ph. D.

7/a/99

Page(s) 15

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Information and are not

releasable.

Micro Review #1

6/11/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-405

ADMINISTRATIVE DOCUMENTS

Verified 2/9/00 RLL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75405/000**
Stamp: **30-JUN-1998** Regulatory Due:
Applicant: **BEDFORD LABS**
270 NORTHFIELD RD
BEDFORD, OH 44146

Priority:
Action Goal:
Brand Name:
Established Name: **CLADRIBINE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **1 MG/ML, 10 ML VIAL**
Org Code: **600**
District Goal: **31-MAY-1999**

FDA Contacts:

M. DILLAHUNT	**(HFD-613)**	**301-827-5846**	**, Project Manager**
E. SCHAEFER	**(HFD-625)**	**301-827-5848**	**, Review Chemist**
M. SMELA JR	**(HFD-625)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 11-AUG-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1519257**
BEN VENUE LABORATORIES INC
270 & 300 NORTHFIELD RD
BEDFORD, OH 441460568

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-AUG-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

MF No: **13006**
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-AUG-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 03-Nov-1999 03:37pm EST
From: Robert West
WESTR
Dept: HFD-611 MPN2 271
Tel No: 301-827-5846 FAX 301-443-3847

TO: Michael Smela (SMELA)

CC:
CC:

Subject: Re: Process Question

Mike:

My advice would be to get the methods validation issues resolved as quickly as possible while they are fresh in our minds. The most timely way to do this is to fax the questions to the firm and request that the firm submit a minor amendment in response. Unfortunately, we'll likely wind uo doing a second T/A letter, but it is a process that we've used before to get repeat T/A's off the books. Luckily, this doesn't happen often.

Bob

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>
>
>
>
>
>Hi...I have a tentatively approved application where the methods validation came
>back with problems.
>
>Do I fax the problems with a request for a minor amendment and then do a 2ND T/A
>or a Minor depending on whether the response is OK or not.
>
>Or do I fax the problems with a request for an unsolicted amendment which will
>not get reviewed until they respond to the T/A letter (maybe years).
>
>Or do I fax the problems and ask that they respond when they respond to the T/A
>letter which again may be years.
>
>A further complication is we need to communicate with the firm but the
>application is not on any que.
>
>This is easy for approved ANDAs since we can do supplements. I do not

know what
>to do with a T/A.
>
>Regards....Mike
>

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 03-Nov-1999 03:24pm EST
From: Michael Smela
SMELA
Dept: HFD-625 MPN2 E236
Tel No: 301-827-5848 FAX 301-594-0180

TO: See Below

Subject: Re: Process Question

Thank You Pat...In this case, an amendment will need to be submitted by the firm.

Mike

Distribution:

TO: Pat Beers-Block (BEERSBLOCKP)

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 03-Nov-1999 01:15pm EST
From: Pat Beers-Block
BEERSBLOCKP
Dept: HFD-640 MPN2 E260
Tel No: 301-827-5849 FAX 301-443-3839

TO: See Below

Subject: Re: Process Question

Mike,

Good questions. We have had this happen so infrequently that we don't have a written procedure (yet!).

We have had a similar situation before that is like this but it was for a fully approved application .
In that case, OGD reviewers/TLs and the Chem. Div II worked closely with the FDA labs performing the analysis and coordinated information with the firm. (NOTE: As it turned out the FDA labs had problems and it was not the procedure.). Susan Rosencrance was the chemist.

Since there will never be situation where an application is on a que as we have ta'd or fully approved the application, in the case of the problems were immediately addressed by the reviewer upon learning of them. I believe it makes sense to handle the work as priority work and address the problems directly. The firm has committed to working with OGD (written commitment from the firm and our letter reaffirms that commitment). I don't know the circumstances re: what happened with this analysis, but in the case of it meant making a series of phone calls, and working with DFS, the FDA labs, and the firm to make certain the analysis was performed correctly by all parties. Your current situation may suggest the same efforts. For product, I don't believe anything needed to be issued to the firm in the end.

You may want to talk to Susan re: her handling of this process. In my opinion, we should look at developing a procedure that will delineate how OGD will consistently handle post approval mv sample problems.

pb2

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what
>to do with a T/A.
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>Regards....Mike
>

Distribution:

TO: Michael Smela (SMELA)

E L E C T R O N I C M A I L M E S S A G E

Date: 03-Nov-1999 11:59am EST
From: Michael Smela
SMELA
Dept: HFD-625 MPN2 E236
Tel No: 301-827-5848 FAX 301-594-0180

TO: Robert West (WESTR)
TO: Pat Beers-Block (BEERSBLOCKP)

Hi...I have a tentatively approved application where the methods validation came back with problems.

Do I fax the problems with a request for a minor amendment and then do a 2ND T/A or a Minor depending on whether the response is OK or not.

Or do I fax the problems with a request for an unsolicted amendment which will not get reviewed until they respond to the T/A letter (maybe years).

Or do I fax the problems and ask that they respond when they respond to the T/A letter which again may be years.

A further complication is we need to communicate with the firm but the application is not on any que.

This is easy for approved ANDAs since we can do supplements. I do not know what to do with a T/A.

Regards....Mike

RECORD OF TELEPHONE CONVERSATION

ANDA 75-405 was tentatively approved 8/31/99 in the absence of methods validation. A MV Report dated 10/22/99 was received from the FDA Pacific Regional Laboratory Northwest, Seattle on 10/27/99. The lab considered Bedford's methods satisfactory with modifications (lab classification 2). The firm received a not approvable minor facsimile because of deficiencies in analytical methods on December 8, 1999. The firm requested a telecon to discuss 1.(b) of the chemistry comments.

1. Regarding analytical method 926-00-024.1, which was submitted in the original ANDA on pages 0691 to 0709:
b. The percent of each individual known impurity should be calculated with respect to the area of that known impurity's standard, rather than the total area.

Mr. Ahmed wanted to know if the percent for each known impurity should be calculated against the standard peak area, or could the peak area of the known impurity be corrected by use of its response factor.

Dr. Schaefer informed him that either approach would be O.K.

DATE
December 9, 1999

ANDA NUMBER
75-405

IND NUMBER

TELECON

INITIATED BY

SPONSOR X

FDA

PRODUCT NAME
Cladribine Injection, 1 mg/mL, 10 mL vial

FIRM NAME
Bedford Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Shahid Ahmed

TELEPHONE NUMBER
(440) 232-3320 EXT 333

SIGNATURE
M.Dillahunt 12/14/99
E. Schaefer

/S/

V:\FIRMSAM\BEDFORD\TELECONS\75405.TC.002.DOC
CC: ANDA 75-405
Chem Div I, T-con Notebook

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-405 **Date of Submission: December 6, 1999**
Applicant's Name: Bedford Laboratories
Established Name: Cladribine Injection, 1 mg/mL
APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (10 mL) Satisfactory as of March 23, 1999 submission.
Carton Labeling: (1 x 10 mL) Satisfactory as of March 23, 1999 submission.
Professional Package Insert Labeling: Satisfactory as of December 6, 1999 submission.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Leustatin®
NDA Number: 20-229
NDA Drug Name: Cladribine Injection
NDA Firm: R.W. Johnson
Date of Approval of NDA Insert and supplement #: February 26, 1993. S-004 and S-007 (SSCBE's)
Pending approval. New Drug expects to approve soon.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. ODE- Expires 2-26-2000, Will not market before this time.	X		

FOR THE RECORD:

1. The reference listed drug for this product is R.W, Johnson Pharmaceutical Research Institute□s Leustatin□(Approved February 26, 1993). However, the firm has submitted a side-by-side compared to a revised insert which appears in the PDR. Team Leader, John Grace, states that new drugs anticipates approval of this revised labeling. Therefore, we will not request the firm to return to the originally approved labeling. ~~NOTE: Full approval for this application can not be granted until we receive documentation from new drugs stating the proposed innovator revisions have been approved. The Orange book name is Cladribine Injectable; Injection. This is not a USP item. The applicant uses Cladribine Injection, 1 mg/mL.~~
   NOTE: The original labeling differs in DOSAGE AND ADMINISTRATION. ~~IV was never in the marketplace.~~ 0.1 mg/Kg/day was original dose. The LLO was requested to submit SSCBE Δing to 0.09/mg/Kg/d. by New Drug
2. The applicant certifies that the New Chemical Entity Exclusivity expired on 2-16-98 and that it will not market until the Orphan Drug Exclusivity expires on 2-26-2000.
   See Vol. 1.1, page 6.
3. The product is manufactured by BenVenue Laboratories, Inc, 270 Northfield Road, Bedford, Ohio 44146, for Bedford Laboratories. No outside firms are utilized. See Vol. 1.1, page 174 & 176.
4. Container/Closure Statement

5. Fished Product-Clear, colorless, sterile, preservative free, isotonic solution. See Vol. 1.1, page 24.
6. Product Line-10 mg(1 mg/mL) of Cladribine as 10 mL filled in a single-use clear Flint glass 20 mL vial individually boxed. See Vol. 1.1, page 45.
7. Components/Composition Statement
   Innovator:
   Active: Cladribine
   Inactive: Sodium Chloride
   Phosphoric acid
   and/or Dibasic Sodium Phosphate to adjust pH
   Applicant:
   Active: Cladribine
   Inactive: Sodium Chloride
   Phosphoric acid
   and/or Dibasic Sodium Phosphate to adjust pH
   Water for Injection qs to 1 mL
   See Vol. 1.1, page 74.
8. Storage/Dispensing Conditions
   NDA: Store Refrigerated 2□ to 8□C(36□ to 46□F). Protect from light during storage.
   ANDA: Same as NDA.

Date of Review: December 10, 1999
Date of Submission: December 6, 1999

Reviewer: **Date:** 12-10-99

Team Leader: **Date:** 12-13-1999

cc:

Concur: [signature] 12/13/99

Verified 8/30/99 Rwd

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75405/000**
Stamp: **30-JUN-1998** Regulatory Due:
Applicant: **BEDFORD LABS**
270 NORTHFIELD RD
BEDFORD, OH 44146

Priority:
Org Code: **600**
Action Goal:
District Goal: **31-MAY-1999**
Brand Name:
Established Name: **CLADRIBINE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **1 MG/ML, 10 ML VIAL**

FDA Contacts: **D. HUIE (HFD-623) 301-827-5848 , Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 11-AUG-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1519257**
BEN VENUE LABORATORIES INC
270 & 300 NORTHFIELD RD
BEDFORD, OH 441460568

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-AUG-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-AUG-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ANDA APPROVAL SUMMARY

ANDA: 75-405	CHEMIST: Eugene L. Schaefer, Ph.D.	DATE: 8/10/1999
DRUG PRODUCT: Cladribine Injection		
FIRM: Bedford Laboratories		
DOSAGE FORM: Injection	STRENGTH: 1 mg/mL, 10 mL per vial	

cGMP:

The facilities were found acceptable on 8/24/98. **A new EER might be needed, if the approval package does not get all the required signatures by 8/24/99.** An EER was re-issued & is acceptable per Aug. 11, 199

BIO:

A waiver was granted 9/24/98.

VALIDATION - (Description of dosage form received by FDA lab same as in firm's ANDA?): Yes

Methods Validation has been started at PRL-NW, Seattle, **but not completed**, per E-mail from Tom Savage 8/10/99.

STABILITY:

The containers in the stability studies are identical to those in the container section.

LABELING:

Container, carton, and insert labeling were tentatively approved on 4/5/99.

STERILIZATION VALIDATION (If applicable):

Satisfactory per review of Lynne Ensor, Ph.D. on 8/6/99.

SIZE OF BIO BATCH (Firm's source of NDS ok?):

SIZE OF STABILITY BATCHES (If different from bio batch, were they manufactured via the same process?):

The size of the stability batch was

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The maximum size of production batches will be The manufacturing process is identical to the exhibit batch.

Signature of chemist: /S/	Signature of supervisor: /S/
Eugene L. Schaefer, Ph.D. '99 /S/	Michael Smela

\\CDV008\WP51F99\FIRMSAM\BEDFORD\LTRS&REV\75405ap.sum

MINUTES OF PHONE CALL

DATE: 8/25/99

SUBJECT: ANDA 75-405 , Cladribine Inj

ORGANIZATION: **Bedford labs**

PARTICIPANTS: Allen Rudman
Dr. Shahed Ahmed

Dr Ahmed was asked if there was a protocol to extend expiry in the application. He said that there was none. He acknowledged that if Bedford wanted to extend the expiry without a protocol they would have to submit a pre-approval supplement.

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75405/000**
Stamp: **30-JUN-1998** Regulatory Due:
Applicant: **BEDFORD LABS**
270 NORTHFIELD RD
BEDFORD, OH 44146

Priority: Org Code: **600**
Action Goal: District Goal: **31-AUG-1999**
Brand Name:
Established Name: **CLADRIBINE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **1 MG/ML, 10 ML VIAL**

FDA Contacts: **D. HUIE** **(HFD-615)** **301-827-5862 , Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 24-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1519257**
BEN VENUE LABORATORIES INC
270 & 300 NORTHFIELD RD
BEDFORD, OH 441460568

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: *April 01, 1999*

To: Food and Drug Administration Pre-approval Laboratory
Philadelphia District Laboratory, HFR-MA160
US Customhouse
2nd and Chestnut Streets, Room 900
Philadelphia, PA 19106
Attention: Wayne T. Smith

EFS 4/1/99

From: Eugene L. Schaefer, Ph.D., Review Chemist, HFD-625

Through: Mujahid Latif Shaikh, Acting, Chemistry Team Leader, HFD-625 Mujahid 4/2/99

Subject: Laboratory Assignments for ANDA Methods Validation (MV)

ANDA No: 75-405 **Product:** Cladribine Injection, 1 mg/mL, 10 mL per vial

Applicant: Bedford Laboratories, A Division of Ben Venue Laboratories, Inc.

The firm has submitted their regulatory methods for this drug product. These proposed regulatory analytical methods should be validated by your laboratory as this subject drug product does not have a USP monograph.

As instructed under the PRE-APPROVAL INSPECTION/INVESTIGATIONS program (CP 7346.832), you are requested to obtain samples of the subject drug product including impurity reference standards (if any) from the applicant at the address given below:

Bedford Laboratories, A Division of Ben Venue Laboratories, Inc.
Attention: Mr. Shahid Ahmed
300 Northfield Road
Bedford, Ohio 44146

Telephone: 440-232-3320
FAX: 440-232-6264

Upon completion of methods validation, please send work sheets, all attachments, conclusions, and recommendations directly to the review chemist at the address given below:

Eugene L. Schaefer, Ph.D.
Office of Generic Drugs, HFD-625
7500 Standish Place
Rockville, MD 20855

Telephone: (301) 827-5771
FAX: (301) 594-0180

Enclosed is one methods validation (MV) package with MV request forms (2871 & 2871a).

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Eugene L. Schaefer, Ph.D. (Reviewing Chemist), HFD- 625 Tel. No. (301) 827-5771
Tel. No. (301) 594-0180 (FAX)
Through: Mujahid Latif Shaikh, Acting (Chemistry Team Leader), HFD- 625 Tel. No. (301) 827-5768

SUBJECT: Methods Validation for ANDA No. 75-405 /S- _____ Amendment Minor
Product: Cladribine Injection, 1 mg/mL, 10 mL per vial
Applicant: Bedford Laboratories, A Division of Ben Venue Laboratories, Inc.
Address: 300 Northfield Road, Bedford, Ohio 44146

TO: ☐ Philadelphia District Laboratory, HFR-MA160 (Pre-Approval Laboratory) Date: 04 / 01 / 99

Date ANDA Received by CDER: June 30, 1998 Chemical/Therapeutic Type: Synthetic anti-cancer agent.
Special Handling Required: Protect from light. Store in refrigerator. Hygroscopic.
DEA Class: Not a controlled substance. PAC: ■ 52832 (ANDA's) ☐ 46832 (NDA's)

This is to confirm the suitability of the proposed manufacturing controls as described in the subject application. The samples identified in the attached Form 2871a (Methods Validation Request and Reporting Record) will be provided to you by the applicant. Please perform the tests indicated in item 3 of 2871a as described in the accompanying MV package, and summarize your laboratory results in item 4. Also, please include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

Because of statutory time limits for processing applications, we request your report to be submitted promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. Please promptly advise the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist.

Upon completion of the requested validation/verification, please assemble the necessary documentation (i.e., the original signed 2871a with original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying memoranda). At the bottom of the report signed by the laboratory director, place the filing code: **"MR/Method Validation Report."** Send by overnight courier to the above reviewing chemist.

ENCLOSURE: Form 2871a and ANDA Methods Validation Package.

METHODS VALIDATION REQUEST AND REPORTING RECORD

ANDA No. 75-405

1. SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
None	None	None

2. Contents of Attached Methods Validation Package ⟹

	PAGE NUMBER(S)		
Statement of Composition of Finished Dosage Form(s)	Original ANDA of	6/29/98,	page 74
Specifications/Methods for New Drug Substance(s)	Amendment of 3/23/99,	5-6, 43-50	
Specifications/Methods for Finished Dosage Form(s)	3/23/99 10, 12, 25-31;	6/29/98	691-709
Supporting Data for Accuracy, Specificity, etc.	3/23/99 33-42;	6/29/98	653-683
Applicant's Test Results on NDS and Dosage Forms	3/23/99 7-9, 13-14		
Other: MS identification of impurity in dosage form		6/29/98	684-690

3. REQUESTED DETERMINATIONS (Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.)

a. Drug Substance

Method BNCH3683-155.1

Assay for Residual Methanol in Cladribine Drug Substance, by Headspace GC Analysis

b. Dosage Form

Method 926-00-024.1

Identification and Quantification of Cladribine and Related Substances in the Cladribine Drug Substance and in Cladribine Injection Drug Product and Stability Testing, by HPLC

4. SUMMARY OF RESULTS (Report individual and average ASSAY results.)

Signature of Analyst:

Date:

DATE	FIELD LABORATORY COPY ROUTING	DATE	☐ DDA or ☐ DRT COPY ROUTING
	Forwarded to Reviewing Chemist		Forwarded to Reviewing Chemist
	Received by Reviewing Chemist		Received by Reviewing Chemist

MR/Method Validation Report (Attach additional pages, if needed.)

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-405 **Date of Submission: March 23, 1999**

Applicant's Name: Bedford Laboratories

Established Name: Cladribine Injection, 1 mg/mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes
If no, list why:

Container Labels: (10 mL) Satisfactory as of March 23, 1999 submission.

Carton Labeling: (1 x 10 mL) Satisfactory as of March 23, 1999 submission.

Professional Package Insert Labeling: Tentatively Satisfactory as of March 23, 1999 submission. See FOR THE RECORD.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Leustatin®

NDA Number: 20-229
NDA Drug Name: Cladribine Injection
NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement #: February 26, 1993. S-004 and S-007 (SSCBE's) Pending approval. New Drug expects to approve soon.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PI?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributed statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opaseals, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. ODE- Expires 2-26-2000, Will not market before this time.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is R.W, Johnson Pharmaceutical Research Institute's Leustatin™(Approved February 26, 1993). However, the firm has submitted a side-by-side compared to a revised insert which appears in the PDR. Team Leader, John Grace, states that new drugs anticipates approval of this revised labeling. Therefore, we will not request the firm to return to the originally approved labeling. NOTE: Full approval for this application can not be granted until we receive documentation from new drugs stating the proposed innovator revisions have been approved. The Orange book name is Cladribine Injectable; Injection. This is not a USP item. The applicant uses Cladribine Injection, 1 mg/mL.
NOTE: The original labeling differs in DOSAGE AND ADMINISTRATION. IV was never in the marketplace.

2. The applicant certifies that the New Chemical Entity Exclusivity expired on 2-16-98 and that it will not market until the Orphan Drug Exclusivity expires on 2-26-2000. See Vol. 1.1, page 6.

3. The product is manufactured by BenVenue Laboratories, Inc, 270 Northfield Road, Bedford, Ohio 44146, for Bedford Laboratories. See Vol. 1.1, page 174.

4. No outside firms are utilized. See Vol. 1.1, page 176.

5. Container/Closure Statement

   Container: Wheaton 2920 20 cc 20 mm Type I Flint Molded.
   Closure: West S127 4416/50 20 mm Gray plug
   Seal: West 4107, Mist gray 20 mm Aluminum Flip off seals.

   See Vol. 1.2, page 583.

6. Finished Product

   Clear, colorless, sterile, preservative free, isotonic solution.

   See Vol. 1.1, page 24.

7. Product Line

   10 mg(1 mg/mL) of Cladribine as 10 mL filled in a single-use clear Flint glass 20 mL vial individually boxed.

   See Vol. 1.1, page 45.

8. Components/Composition Statement

Innovator:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phosphate to adjust pH

Applicant:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phospate to adjust pH
Water for Injection qs to 1 mL

See Vol. 1.1, page 74.

9. Storage/Dispensing Conditions

NDA: Store Refrigerated 2° to 8°C(36° to 46°F). Protect from light during storage.

ANDA: Same as NDA.

Date of Review: March 26, 1999
Date of Submission: March 23, 1999

Reviewer: **Date:** 4/5/99

Team Leader: **Date:**

4-5-1999

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cc:

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-405 **Date of Submission: June 29, 1998**

Applicant's Name: Bedford Laboratories

Established Name: Cladribine Injection, 1 mg/mL

Labeling Deficiencies:

1. GENERAL COMMENTS:

2. CONTAINER

   a. Revise "For IV Infusion" to read "MUST BE DILUTED PRIOR TO IV INFUSION".

3. CARTON

   a. Revise "For IV Infusion" to read "MUST BE DILUTED PRIOR TO IV INFUSION".

4. INSERT

   a. TITLE

      We encourage the inclusion of "℞ only".

   b. We encourage the relocation of "℞ only" to the TITLE section.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: [redacted]
Stamp: 30-JUN-1998 Regulatory Due:
Applicant: **BEDFORD LABS**
270 NORTHFIELD RD
BEDFORD, OH 44146

Priority: Org Code: **600**
Action Goal: District Goal: **31-AUG-1999**
Brand Name:
Established Name: **CLADRIBINE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **1 MG/ML, 10 ML VIAL**

FDA Contacts: **D. HUIE** **(HFD-615)** **301-827-5862 , Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848 , Team Leader**

Overall Recommendation:

[redacted] **BROGIO (HFD-324) 301-827-0062**

Establishment: **1519257**
BEN VENUE LABORATORIES INC
300 NORTHFIELD RD
BEDFORD, OH 441460568

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

[redacted]

F No: **13006**
DA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-405 **Date of Submission: June 29, 1998**

Applicant's Name: Bedford Laboratories

Established Name: Cladribine Injection, 1 mg/mL

Labeling Deficiencies:

1. GENERAL COMMENTS:

2. CONTAINER

   a. Revise "For IV Infusion" to read "MUST BE DILUTED PRIOR TO IV INFUSION".

3. CARTON

   a. Revise "For IV Infusion" to read "MUST BE DILUTED PRIOR TO IV INFUSION".

4. INSERT

   a. TITLE

      We encourage the inclusion of "℞ only".

   b. We encourage the relocation of "℞ only" to the TITLE section.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? Yes No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the PTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (PTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting ink? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (PTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and data study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: PTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. ODE- Expires 2-26-2000, Will not market before this time.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is R.W, Johnson Pharmaceutical Research Institute's Leustatin™(Approved February 26, 1993). However, the firm has submitted a side-by-side compared to a revised insert which appears in the PDR. Team Leader, John Grace, states that new drugs anticipates approval of this revised labeling. Therefore, we will not request the firm to return to the originally approved labeling. NOTE: Full approval for this application can not be granted until we receive documentation from new drugs stating the proposed innovator revisions have been approved. The Orange book name is Cladribine Injectable; Injection. This is not a USP item. The applicant uses Cladribine Injection, 1 mg/mL.
NOTE: The original labeling differs in DOSAGE AND ADMINISTRATION. IT was never in the marketplace.

2. The applicant certifies that the New Chemical Entity Exclusivity expired on 2-16-98 and that it will not market until the Orphan Drug Exclusivity expires on 2-26-2000. See Vol. 1.1, page 6.

3. The product is manufactured by BenVenue Laboratories, Inc, 270 Northfield Road, Bedford, Ohio 44146, for Bedford Laboratories. See Vol. 1.1, page 174.

4. No outside firms are utilized. See Vol. 1.1, page 176.

5. Container/Closure Statement

   Container: Wheaton 2920 20 cc 20 mm Type I Flint Molded.
   Closure: West S127 4416/50 20 mm Gray plug
   Seal: West 4107, Mist gray 20 mm Aluminum Flip off seals.

   See Vol. 1.2, page 583.

6. Finished Product

   Clear, colorless, sterile, preservative free, isotonic solution.

   See Vol. 1.1, page 24.

7. Product Line

   10 mg(1 mg/mL) of Cladribine as 10 mL filled in a sinle-use clear Flint glass 20 mL vial individually boxed.

See Vol. 1.1, page 45.

8. Components/Compossition Statement

Innovator:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phosphate to adjust pH

Applicant:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phospate to adjust pH
Water for Injection qs to 1 mL

See Vol. 1.1, page 74.

9. Storage/Dispensing Conditions

NDA: Store Refrigerated 2° to 8°C(36° to 46°F). Protect from light during storage.

ANDA: Same as NDA.

Date of Review: September 23, 1998
Date of Submission: June 29, 1998

Reviewer: **Date:** 9/23/98

Team Leader: **Date:** 9/23/98

---

cc:

l.L

Application: **ANDA 75405/000**
Stamp: **30-JUN-1998** Regulatory Due:
Applicant: **BEDFORD LABS**
270 NORTHFIELD RD
BEDFORD, OH 44146

Priority:
Action Goal:
Brand Name:
Established Name: **CLADRIBINE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **1 MG/ML, 10 ML VIAL**

Org Code: **600**
District Goal: **31-AUG-1999**

FDA Contacts: **D. HUIE** **(HFD-615)** **301-827-5862** **, Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848** **, Team Leader**

Overall Recommendation:

Establishment: **1519257**
BEN VENUE LABORATORIES INC
300 NORTHFIELD RD
BEDFORD, OH 441460568

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **31-JUL-1998**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **31-JUL-1998**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Telecon

Date: 071498

Time: 1400 H

ANDA #: 75-405

Firm: Bedford Labs.

Drug: Cladribine Injection, 1 mg/mL, 10 mL vial

Participants: Gregg Davis, FDA and Shahid Ahmed

Phone #: 440-232-3320 ext. 333

Agenda:

I called Shahid and asked for an additional piece of info. The application did not contain a side-by-side labeling comparison for the carton and vial labels. It only contained this comparison for the insert. He said it was an oversight in copying and he will fax the info and follow with a hard copy.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-405

CORRESPONDENCE

BEDFORD
LABORATORIES™

December 16, 1999

Minor Amendment

Office of Generic Drugs
Center for Drug evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N | Rm

Re: ANDA 75-405 / Minor Amendment
Product: Cladribine Injection, 1 mg/mL, 10 mL per vial

Dear Sir/Madame:

We wish to amend our tentatively approved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Minor Deficiency of December 8, 1999 after the method validation was completed.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

1.a. The term "conc" has been replaced with the term "amount". The revised method is provided in Attachment II.

1.b. The impurity calculation has been revised. Any detected known impurities in the sample will be calculated with respect to the areas of that particular known impurity standard and the appropriate concentrations, and not by area normalization. The method has been revised accordingly and is provided in Attachment II.

2. The specification for the residual solvent level has been revised to not more than to be consistent with the units expressed in the method. The revised specifications are provided in Attachment III.

3. This was the first lot of Cladribine produced at Ben Venue. The visible particulate appears to be an isolated event unique to this lot. The subject lot (0926-49-51852) was a small stability batch of approximately 700 vials manufactured in February 1998. A total of thirty six vials were pulled by the Production Inspectors for visible particles.

CENTER FOR DRUG RECD 1/1 1999 OGD EVALUATION AND RESEARCH

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

Our investigation found no root cause for the visible particle in the vial found by the FDA laboratory, however, it should have been caught during Production's 100% visible inspection. It is possible that during the inspection process, the particle was hung up on the stopper and not observed during the manual inspection. After Production's 100% inspection, the lot passed a Mil-Standard Inspection by Quality Assurance with no defects found.

A review of the batch record found no manufacturing issues that could have contributed to the defect. A re-inspection of all remaining vials left in inventory found no visible particles. Moreover, during the FDA inspection, Fred Lochner (FDA district investigator) inspected 200 vials of cladribine drug product stored under refrigerated conditions and found all vials to be acceptable.

An evaluation of other products filled using the same vial/closure system during the same timeframe as Cladribine lot 926-49-51852 revealed no particulate issues or problems indicative of a system deficiency.

BVL manufactured a second batch of Cladribine in April 1999 (a different presentation, 8 ml per vial) which met all established specifications and did not exhibit an abnormal particulate level.

In conclusion, we could not determine an exact cause for the black particles. This appears to be an isolated incident in which a single known defect was missed during the manual inspection. The Production Inspection Department was made aware of this missed defect.

We trust this meets with your approval. If you have any additional questions or concerns, I can be reached by phone at 440-232-3320, ext. 333 or by fax at 440-232-2772.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director of Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
LABORATORIES™

December 6, 1999

Minor Amendment
Labeling

ORIG AMENDMENT
MAM

Office of Generic Drugs
Center for Drug evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-405 / Minor Amendment
Product: Cladribine Injection, 1 mg/mL, 10 mL per vial

Dear Sir/Madame:

We wish to amend our tentatively approved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to identify any changes in the conditions under which the product was tentatively approved.

There have been no changes to the chemistry, manufacturing, controls, nor to the labeling since the time the tentative approval was granted. Bedford Laboratories™ is supplying 12 copies of the final printed vial labels, cartons, and package inserts.

We trust this meets with your approval. If you have any additional questions or concerns, I can be reached by phone at 440-232-3320, ext. 333 or by fax at 440-232-2772.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed

Shahid Ahmed
Director of Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG
DEC 6 1999

BEDFORD LABORATORIES™

Response to Microbiology Deficiencies

August 2, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

FA

RE: **ANDA 75-405/Facsimile Amendment**
Product: **Cladribine Injection, USP; 1 mg/mL, 10 mL per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Facsimile Deficiency of July 21, 1999.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. Microbiology Deficiencies:

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

8/2/99

BEDFORD LABORATORIES™

8. The reference to "exposure to the terminal sterilization process" was inadvertently copied from a format used to create the report. It has been removed from the report and the corrected page is provided in Attachment V.

B. Acknowledgements

Bedford Laboratories™ acknowledges that a satisfactory Methods Validation is needed to support the ANDA and that a study has been scheduled.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
LABORATORIES™

May 10, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AM

RE: **ANDA 75-405/Facsimile Amendment**
Product: **Cladribine Injection, USP; 1 mg/mL, 10 mL per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Facsimile Deficiency of April 27, 1999.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. Chemistry Deficiencies:

B. ACKNOWLEDGEMENTS

1. Bedford Laboratories™ acknowledges that the labeling portion of the amendment is still pending.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
LABORATORIES™

March 23, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

AM

RE: **ANDA 75-405/Minor Amendment**
Product: **Cladribine Injection, USP; 1 mg/mL, 10 mL per vial**

not in USP, as of 3/29/99.

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Minor Deficiency of February 12, 1999. ESS

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. Chemistry Deficiencies:

B. ACKNOWLEDGEMENTS

1. Bedford Laboratories™ acknowledges that the sterility assurance review is still pending.

2. Bedford Laboratories™ acknowledges that careful attention must be paid when photocopying original documents to create readable copies.

3. The specifications given on page 723 of the application are for the Drug Product and were mistakenly titled as Shelf-Life specifications. The page has been corrected and is provided in Attachment XI

4. Bedford Laboratories™ acknowledges that a methods validation is required to support the ANDA and will be scheduled once analytical issues are resolved.

5. All deficiencies cited have been corrected. Please refer to Attachment XII for twelve copies of final printed vial labels, carton and package insert labeling for review. Also

BEDFORD
LABORATORIES™

located in Attachment XI are annotated side-by-side comparisons of the proposed final printed package insert with the last draft package insert.

6. Bedford Laboratories™ acknowledges that a satisfactory establishment evaluation from the Office of Compliance is necessary for approval.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD LABORATORIES™

July 14, 1998

Mr. Greg Davis
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

NC
NAT 7/21/98
Gregory S. Davis

Re: **Telephone Amendment** / 75-405
Product: **Cladribine Injection, - 1 mg/mL, 10 mL vials**

Dear Mr. Davis:

Please find enclosed the side by side comparison of the vial labels and carton labeling of the listed drug versus the proposed drug labeling requested in the telephone communication of July 14, 1998.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 439-6398 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
JUL 16 1998
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

ANDA 75-405

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

31

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated July 14, 1998 and your correspondence dated July 21, 1998.

NAME OF DRUG: Cladribine Injection, 1 mg/mL

DATE OF APPLICATION: June 29, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 30, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

/S/
Jerry Phillips 7/31/98
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BEDFORD
LABORATORIES™

505(j)(2) OK 7/29/98
Gregory S. Davis

June 29,1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
JUN 30 1998
GENERIC DRUGS

RE: Abbreviated New Drug Application
PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL vial

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Cladribine Injection, 1 mg/mL; 10 mL vial. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Ortho Biotech, Leustatin® Injection.)

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of our application (Cladribine Injection, 1 mg/mL; 10 mL vial). The drug product is a solution intended solely for intravenous administration and it contains the active ingredient in the same concentration as in the listed drug.

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

Three copies of analytical methods which were used to test this product and an analytical method validation package are enclosed separately along with this application.

One copy of the Microbiological Validation, along with the drug product specification, stability protocol, and the package insert are enclosed separately with this application. This drug product was aseptically filled.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-232-3320, ext. 333 (direct) and (440)-439-6398 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.